

ORSETT BRIEFING PAPERS FOR PSYCHOLOGISTS

No.5 - Basic Pharmacokinetics

Introduction

Pharmacokinetics is the study of the action of a drug upon the body. There are a number of steps between the intake of the drug, and its place of action, say, in the brain.

This includes the concentration at the site of action as determined by the drug's absorption, distribution, biotransformation (breakdown of the active elements of the drug), and excretion through the body. The mode of delivery (eg: oral) also influences this process.

Drugs that work on the central nervous system tend to be agonists or antagonists. Agonists stimulate the receptor at the synapse, thus producing an effect without the presence of the neurotransmitter. Antagonists prevent the neurotransmitter from stimulating the receptor at the synapse.

Absorption

Absorption is the process by which the active ingredients of the drug get into the bloodstream. Bioavailability refers to the fraction of the dose absorbed into the blood. For example, for two anti-psychotics, chlorpromazine it is 25-30%, and haloperidol 65%. With lithium, complete absorption takes 6-8 hours.

Factors which influence this process include:

i) destruction by stomach acid for drugs administered by the mouth as they pass through the stomach (low bioavailability);

ii) formulation of the drug;

iii) food;

iv) co-administration of drugs;

v) metabolism of the gut flora, intestinal wall and liver; eg: fluoxetine (anti-depressant) metabolised by demethylation, and in liver by norfluoxetine.

"First-pass metabolism" is the metabolism of the drug en route through the stomach. Drugs with high "first-pass metabolism" have large amounts lost before the site of action; eg: chlorpromazine (anti-psychotic); imipramine and nortriptyline (anti-depressants).

After the drug is absorbed into the bloodstream, it is distributed to cells by fluid movements within the body (eg: water movement between cells). The passage of drugs into the brain is determined by the blood-brain barrier.

Distribution

This process is the spread of the drug to the tissues (ie: the site of action). This stage can include biotransformation. Drugs will be given a measure "V", which means the "volume of distribution". This is defined as the apparent volume of fluid into which the drug distributed based on the amount of the drug in the body and measured by the concentration in the plasma or serum. A low V means a high concentration in the blood; eg: nortriptyline (anti-depressant) $V = 20 \text{ L/kg}$. Lithium has an initial V of 0.5 L/kg , and it peaks at $0.7\text{-}0.9 \text{ L/kg}$.

The figure for V is important because the amount of dose given is linked to the strength of the effect required. The "loading dose" (ie: the immediate response required) is calculated as: $V \times \text{desired concentration}$, and is often written as mg/kg dose. A much larger dose may be given at the beginning of the treatment, then less for the maintenance of the effect.

The traditional measure of the concentration of the drug in the blood has been questioned by findings from studies using modern technology. A study, using a type of brain scan known as magnetic resonance spectroscopy (MRS), found that brain lithium concentration was half that in the blood measurements. In other words, less of the drug was reaching the area of the body that mattered (ie: the brain) despite circulating in the blood. This may be due to the molecules of the drug being unable to

cross the brain-blood barrier ¹.

The same technique of MRS has shown that it takes six months of steady use of fluoxetine (anti-depressant) to reach maximum concentration in the brain (which is twenty times the serum concentration) ².

Clearance

Clearance is the process of the removal of the drug from the body. Technically, the sum of all drug elimination processes (eg: liver metabolism, renal excretion), or the theoretical volume of fluid from which the drug completely removed in a given period of time.

This is important either to remove the drug from the body, or to know how often the drug has to be taken (or how much) in order to maintain the strength of the effect.

Intravenous infusion (ie: continuous) by drip-feed, for example, produces a balance between input (dosing rate) and output (elimination). This gives a "steady-state concentration" (C_{ss}). Oral administration produces a series of fluctuations with increased action after taking and decline of the effect as time passes (figure 1).

It is important to calculate the average steady-state concentration (C_{ss av}), which is one third of the way between the troughs and peaks of oral administration. The following equation is used:

$$(1) \quad \text{oral C}_{ss \text{ av}} = \frac{F \times \text{dose}}{\text{clearance} \times \text{dosage interval}}$$

F = fraction of dose absorbed into blood
dose = amount of drug given
clearance = time taken for drug to pass through the body
dosage interval = how often drug given

Thus to maintain the effect of the drug:

$$(2) \quad \text{oral maintenance} = \frac{\text{clearance} \times \text{desired C}_{ss \text{ av}} \times \text{dosage interval}}{F}$$

¹ Renshaw, P.F & Wicklund, S (1988) In vivo measurement of lithium in humans by nuclear magnetic resonance spectroscopy, Biological Psychiatry, 23, 465-475.

² Sadock, B.J & Sadock, V.A (2003) Kaplan and Sadock's Synopsis of Psychiatry (9th ed) , Philadelphia: Lippincott Williams & Wilkins.

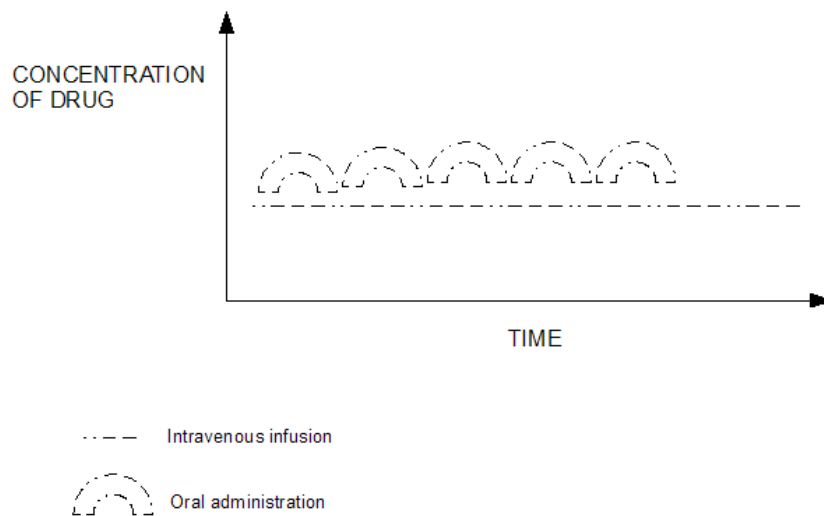


Figure 1 - Differences in drug concentration based on type of administration.

Dose-response relationships

The effectiveness or efficacy of a drug will be influenced by the side effects produced. The "therapeutic index" of a drug is the difference between the concentration that produces the desired effects, and the concentration that produces adverse effects.

While the "therapeutic range" is the difference between the "minimum useful effect" (where the drug first has a positive effect), and the "maximum tolerated adverse effects" (where side effects become greater than the positive effects). These figures are calculated statistically, rather than based on the views of patients.

EXAMPLES OF MINIMUM EFFECTIVE THERAPEUTIC DOSES OF ANTI-PSYCHOTICS (mg)

Chlorpromazine	100
Trifluoperazine	5
Quetiapine	150

SOURCES

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An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

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